REMARKS

Summary of the Office Action

Claims 22-32 are under examination in the present office action. Claims 22-32 stand rejected under 35 U.S.C. § 112, first paragraph on enablement and written description grounds. Each of these rejections is addressed as follows.

Cross-reference to related applications

As requested, applicants have amended their specification to update the priority information of this application.

Amendment

New claim 33 has been added which is directed to a method "which involves preventing and/or treating disseminated intravascular coagulation [(DIC)]". Support for this amendment is found in the specification, for example, at paragraph [0059] of applicants' published application, 2003 0175268 A1. Applicants note that preventing and/or treating DIC according to the methods of the invention is demonstrated in the application in Examples 5 and 6, whereby inhibition of FVIII, either by antibodies or in knock-out mice, results in a reduction of thrombin formation. Applicants also note that DIC is a pathophysiological process (involving excess coagulation) which is one of the most prominent features of sepsis. No new matter has been added by the

present amendment.

Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 22-32 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that applicants' specification does not reasonably provide enablement for the prevention or treatment of SIRS with generic antibodies that bind the C1 domain of FVIII. For the following reasons, this rejection should be withdrawn.

Applicants note that the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). Those skilled in the art routinely screen many antibodies in order to isolate one having the desired effect; such screening is routine in the art and does not constitute undue experimentation.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, as is the situation in the present application. There are several factors to be considered when determining whether the specification is enabled and whether any

necessary experimentation is "undue." These factors include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention. Applicants respectfully submit that one skilled in the art would not have to use undue experimentation to make and use the invention falling within the scope of the pending claims.

In this case, the state of the prior art and the level of ordinary skill is such that the production of an antibody (e.g., a monoclonal antibody against factor VIII or an antigen binding fragment of the monoclonal antibody, where the antibody or fragment is capable of being able to recognize epitopes located in the C1 domain of factor VIII) is merely routine. Any degree of unpredictability is counterbalanced by the fact that the present specification not only provides a high level of explicit direction as to how to make and use and screen antibodies falling within the scope of the claims but also provides working examples.

With respect to the Examiner's statement found on page 5 of the Office action, that "applicants' claimed method appears to work because the administered monoclonal antibody interferes with the ability of FVIII to participate in the coagulation cascade, thus preventing systemic problems with excessive coagulation that often develop in patients suffering from SIRS/Sepsis ... and ... sepsis can occur in patients with impaired coagulation", applicants respectfully

note that the method of the claimed invention is not based on excessive coagulation. Anti-FVIII antibodies prevent excessive thrombin and consumption of APC, which plays a role in inflammation and immunity, in addition to its role in coagulation. It is the balance between thrombin and protein C that is relevant, not just excessive coagulation. Nevertheless, as in most patients, thrombin formation will lead to excessive coagulation, which will also be prevented by the methods of the present invention.

In further reasoning that applicants' claim is not broadly enabled, the Examiner, in the context of hemophiliacs, on page 6, states:

> It is known that thrombin can be generated by many pathways, some of which do not require FVIII [citations omitted]. As such, coagulation can occur even in the presence of FVIII inhibitors (see also lines 31 and 32 of page 4 of the specification), and therefore SIRS/sepsis can also occur in the presence of FVIII inhibitors.

Applicants respectfully note that the Examiner's reasoning is incorrect. While excessive thrombin formation is an important aspect of sepsis in non-hemophiliac patients, this is not the case in hemophiliacs, as their blood-clotting is disturbed (in this regard applicants note that the Cobb publication, mentions that the hemophiliac patient was administered prothrombin, and the Ferenz publication refers to administration of plasma to maintain clotting.). Moreover, applicants' specification states that "some coagulation may occur in the absence of FVIII", but does not refer to excessive coagulation as often seen in sepsis.

Furthermore, the Examiner's concern, expressed on page 6, that "in order to

prevent SIRS/sepsis, therapy would need to begin before the condition was diagnosed and the disclosure does not appear to teach how to select patients that will or will not develop SIRS/sepsis before the signs and symptoms of these condition are clinically apparent" is unwarranted. In this respect, applicants note that SIRS is not a one-step process, it is a condition which evolves with time. The coagulation process includes a positive feedback loop. Thrombin itself activates FVIII, which in turn, by binding to vWF generates more thrombin. In non-hemophiliac patients, FVIII is continuously produced and recruited in the coagulation/inflammation process during SIRS. FVIII is also an acute-phase reagent produced by the liver whenever there is inflammation. By inhibiting FVIII activity, the positive feedback mechanism which amplifies the signal is interrupted. Thus, FVIII inhibition is of interest both at the onset of the process and once the process is ongoing.

Applicants also note that the Examiner's reliance on exceptional cases of sepsis in hemophiliacs to support the non-enablement of the claimed methods is inappropriate. To this end applicants note that Examiner has provided no evidence that the claimed methods would not be useful in non-hemophiliacs. In addition, even assuming *artguendo*, that treatment of hemophiliacs would not be useful, applicants note that the law is clear: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. It is not a function of the claims to specifically exclude ... possible inoperative

substances...." [citations omitted.] *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, 750 F.2d 1569 (Fed. Cir. 1984).

In connection with the Examiner's assertion that "it does not appear that animal model systems of sepsis have predictive value in determining clinical effectiveness in human sepsis", applicants submit that if the enablement requirement for treatment methods in humans were erroneously interpreted to require a "perfect" animal model for treating SIRS/sepsis then the scope of patentable subject matter would be greatly diminished because there are few, if any, human diseases for which a perfect non-human animal model exists. Contrary to the Examiner's reliance on Reidemann, applicants have submitted evidence of reliable experimental animal models for testing the effects of compounds in treating sepsis (see, for example, Yan et al, *Nature Medicine* 10:161-167, 2004 and Martinell et al., *Eur Surg. Res.* 17:160-6, 1985). Moreover, the Examiner relies on Riedmann for the proposition that "extrapolation [of findings in animal models] may not be valid." Riedmann does not indicate that such model systems are never valid. Applicants also again submit that numerous therapeutic methods have been patented without the existence of such a "perfect" model. See, for example, US 6,881,408, US 6,984,649, US 6,989,401, and US 7,008,962; each of which includes claims to the treatment of sepsis and is based on the absence of in vivo data or animal models.

Turning to the Examiner's assertion, found on page 10, stating that "administration of KRIX-1 or any other anti-FVIII antibody may not be effective due to

the presence of preformed anti-idiotypic antibodies present in the patient's circulation" is speculation. All of applicants' experiments with Krix-1 were performed with plasma pool, and no prevention of activity has been observed. Moreover, applicants point out that healthy individuals have inhibitor antibodies that are presumed to be in germline configuration, namely without the mutation in CDR induced by contact with antigen (FVIII) in the presence of effector T cells (as is the case in hemophilia patients with inhibitors or when obtained by immunization of animals).

The enablement requirement of § 112, first paragraph has been satisfied by Applicants, and the rejection of claims 22-31 should be withdrawn.

Written Description

Claims 22-32 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. For the following reasons, this rejection should be withdrawn.

Applicants' specification conveys, with reasonable clarity to the skilled persons, that the inventors possessed the presently claimed invention for all of the reasons previously made of record in this case.

In connection with the Examiner's specific comments on the Gilles publication, applicants note that Gilles indeed indicates that in hemophiliac patients, other anti-

FVIII antibodies are made, which do not interfere with FVIII function. In the context of administration of FVIII to hemophiliacs, this is potentially important, as binding of these antibodies to FVIII, even if they do not inhibit FVIII activity, can potentially interfere with the clearance rate of infused FVIII. However, this is not relevant to the present discussion. Gilles does not suggest that these non-inhibitory antibodies are directed against the C1 domain. Thus, the observation by Gilles is irrelevant to the present discussion. Applicants have demonstrated two antibodies capable of binding to the C1 domain and capable of partially inhibiting Factor VIII. The Examiner has presented no clear argument why further antibodies directed against the C1 domain of factor VIII would not have these same properties.

The written description requirement of § 112, first paragraph has been satisfied by Applicants, and the rejection of claims 22-31 should be withdrawn.

Conclusion

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested. If the Office does not concur, an interview with the undersigned is hereby requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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